Remarks/Arguments

Claims 39-46 and 49-51 are pending in this application and are rejected on various grounds. Claims 1-38, 47-48 had been canceled previously without prejudice or disclaimer. Applicants note the withdrawal of the objection to the specification, and the rejection to the claims under 35 USC § 112, second paragraph. The rejections to the remaining claims are respectfully traversed.

Priority

The Examiner states that Applicants are only entitled to the 2/22/00 priority of application PCT/US00/04414 since a conclusion of utility was not reached based on the stimulatory activity demonstrated in the MLR assay. As discussed below, Applicants maintain that the data generated in the MLR assay (Example 74), first disclosed in U. S. Application Serial No. 60/100,858 filed September 17, 1998, establish patentable utility for the invention claimed in this application, therefore the effective filing date of the present application is September 17, 1998. The Examiner's reasoning will be addressed in Applicants' response to the Section 112 rejections below.

Claim Rejections – 35 USC § 112

Claims 39-43, 50-51 were rejected under 35 USC § 112, first paragraph, allegedly for lack of enablement at the time the application was filed. Applicants respectfully traverse these rejections.

The Examiner acknowledges that the specification is enabling for a polypeptide having at least 80% sequence identity to SEQ ID NO: 4, wherein the polypeptide which inhibits VEGF stimulated proliferation of adrenal cortical capillary endothelial cells. However, the Examiner alleges that the specification "does not provide enablement for a polypeptide of SEQ ID NO:4, which is capable of stimulating proliferation of T lymphocytes."

Earlier, under the section of priority (see Office action, page 3, line 8-10), the Examiner alleged that "the MLR assay is an artificial *in vitro* system that does not provide for specific conditions or specific (real-life) diseases for which the claimed invention would predictably function". In support of this position, the Examiner quoted Kahan (Cur. Opin. Immunol. 4:553-560, 1991) for its statement that "no *in vitro* assay predicts or correlates with *in vivo*

immunosuppressive efficacy," and cited Piccotti *et al.* (*Transplantation* 67:1453-1460, 1999) and Campo *et al.* (*Biological Trace Element Res.* 79:15-22, 2001) as allegedly demonstrating that the MLR assay "which is recognized for determining histocompatibility, does not appear to be predictive of general immune responses *in vivo*." The Examiner added that the MLR assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. Therefore, the "ability of the claimed invention to stimulate proliferation in the MLC [MLR] assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell." Lastly, the Examiner noted that "the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion".

Applicants respectfully disagree and, again, traverse the rejection.

The mixed lymphocyte reaction (MLR) is a well-established *in vitro* assay for assessing the ability of a test compound to stimulate or suppress T cell proliferation, and consequently, for assessing the immune response of an individual. The assay is well-described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc., which is referenced in Example 74, and, the entire content of which is expressly incorporated by reference into the disclosure of the present application. In brief, in this method, an immune response results upon mixing T cells from antigenically distinct individuals under cell culture conditions. An MLR reaction can be monitored qualitatively, for example, by following the incorporation of tritiated thymidine during DNA synthesis, or, by observing blast formation, or by other methods well known in the art.

The statement cited from Kahan that "no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy," has no direct bearing on the question whether the MLR assay can be reliably used to assess the immunostimulatory activity of a test compound. However, even in the context of immunosuppression, Kahan's quoted statement contradicts well established scientific wisdom. The MLR assay has been extensively used and is the best *in vitro* model for screening immunosuppressive agents for use in the prevention of graft-versus-host disease and graft rejection. It is well known that the transplantation of tissues or organs between individuals with MHC incompatibilities quickly activates the recipient's immune system which

then attempts to destroy the transplanted tissue or organ. Transplantation across minor histocompatibility loci generally induces a more indolent response. Physicians analyze the major and minor histocompatibility differences to predict the success of the graft and to adjust the aggressiveness of immunosuppressive therapy.

Inhibitors of MLR find utility in suppressing unwanted immune response, and thus suppresses unwanted graft rejection. For example, the ability of tepoxalin, an immunomodulatory compound, to suppress graft-versus-host reaction, has been demonstrated using the MLR assay (Fung-Leung *et al.*, *Transplantation* 60:362-8 (1995)). Other immunosupressants have also been routinely identified using the MLR assay. For example, the immunosuppressive efficacy of SNF4435 and D, produced by a strain of Streptomyces spectabilis, has been tested using the MLR assay. As recently as 2002, the immunosuppressive effect of tautomycetin (TMC) was assessed with mixed lymphocyte reactions, and confirmed *in vivo* using TMC-treated rats that received a heterotopic cardiac allograft (Shim *et al., Proc. Natl. Acad. Sci USA* 99(16):10617-10622 (2002)). The authors were confident to conclude from the MLR data : "TMC has the capacity to inhibit the intracellular signaling pathway leading to T cell activation and proliferation . . . " (page 10621, second column).

In conclusion, contrary to Kahan's cited statement and the Examiner's position, the art as a whole clearly establishes that the mixed lymphocyte reaction (MLR) is a widely used *in vitro* assay for identifying immunosuppressant compounds.

Since the assay measures the immunomodulatory activity of the compounds tested, it is just as suitable to assess whether a compound is capable to stimulate lymphocyte proliferation as for assessing a test compound's immunosuppressive activity.

The Examiner states that the specification does not provide any "real-life" diseases where the stimulation of lymphocyte proliferation would be beneficial. The teachings of the specification should be evaluated through the eyes of one skilled in the pertinent art at the effective filing date of the present application. In 1998 it was well known in the art, as it is today, that T-cells are highly instrumental in the body's natural defense mechanism fighting infections. For example, viral infections, such as HIV infection, are well known to result in reduced T cell count. Indeed, the count of T-cell lymphocytes is a generally accepted measure of the extent and seriousness of HIV infection and resultant AIDS. Accordingly, stimulators of T-

cell proliferation find utility in fighting viral infections, including retroviral infections, such as HIV infection or Epstein-Barr infection.

Accordingly, the positive results obtained in this assay clearly establish the stated utility for the polypeptides claimed in the present application, and the specification, in turn, enables one skilled in the art to use the compounds for the asserted purpose.

The Examiner's reference to the lack of data in the specification that would enable one skilled in the art "to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention" is believed to be misplaced.

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." The Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has ***asserted*** that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." (Emphasis added.) By the foregoing arguments and supportive evidence Applicants have established that the MLR reaction is a generally recognized assay to assess the immunomodulatory, e.g. immunostimulatory activity of a test compound. Accordingly, absent evidence to the contrary, Applicants' assertion that the PRO217 polypeptide is capable of stimulating lymphocyte (T cell) proliferation should be accepted on its face, without any further supportive evidence. However, the specification goes beyond a mere assertion. The specification teaches that "increases of greater than or equal to 180%" were preferred (see page 209, line 17) which is an example of a result that is considered significant. In view of this teaching, a person skilled in the art would reasonably accept that Applicants' statement concerning the T lymphocyte stimulatory activity is based on solid scientific data. For the same reason, one skilled in the art at the priority date of the present application would have reasonably accepted that Applicants were in the possession of the invention as claimed.

In view of the foregoing arguments and submitted evidence, the Examiner is respectfully requested to reconsider and withdraw the present rejections.

Claim Rejections - 35 USC § 102

Claims 39-43 and 44-46, 49 were rejected under 102 (a) as allegedly being anticipated by Hsieh *et al.* (Nature 398: 431-36, 1999) which discloses a polypeptide with 99.7% sequence identity to SEQ ID NO: 4 of the present application.

Once again, in view of the discussions above, the "stimulation of proliferation of T-lymphocytes assay" provides patentable utility and has a priority date of September 17, 1998. The effective reference date of Hsieh is 1999 which is after the effective filing date of the present application. Thus, Applicants submit that Hsieh is not a proper prior art reference under § 102(a).

Hence, Applicants respectfully request withdrawal of this rejection.

Claims 39-43, 44-46 and 49 were rejected under 102 (b) as allegedly being anticipated by Brewer *et al.* (WO 98/54963; published 12/10/1998) which discloses a polypeptide approximately 99% identical to polypeptide of SEQ ID NO: 4 of the present application.

Again, as discussed above, the effective filing date of the present application is September 17, 1998. The effective reference date of Brewer is 12/10/1998 which is after the effective filing date of the present application.

Thus, Applicants submit that Brewer is not proper prior art under §102(b) or 102(a) and respectfully request withdrawal of this rejection.

Claim Rejections - 35 USC § 103

Claims 44-46, 49 were rejected under 103 (a) as allegedly being obvious over Hsieh *et al.* (Nature 398: 431-36, 1999) which discloses a polypeptide with 99.7% sequence identity (differs by one amino acid) to SEQ ID NO: 4 of the present application.

Also, Claims 44-46, 49 were rejected under 103(a) as allegedly being obvious over Brewer *et al.* (WO 98/54963; published 12/10/1998) which discloses a polypeptide approximately identical to SEQ ID NO: 4 (differs by 2 amino acids) of the present application.

Since both the references cited above have effective reference dates (1999 for Hsieh and 12/10/1998 for Brewer) after the effective filing date of the present application, namely September 17, 1998, Applicants submit that neither Hsieh nor Brewer are prior art under § 103(a) and respectfully request withdrawal of this rejection.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C7).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: September 8, 2003

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